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Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/078379 A1

(54) Title: AMORPHOUS Hmg-CoA REDUCTASE INHIBITORS OF DESIRED PARTICLE SIZE

(57) Abstract: A process for the preparation of amorphous HMG-CoA reductase inhibitor and its hydrates thereof of desired particle size, which comprises: (a) dissolving the HMG-CoA reductase inhibitor in a hydroxylic solvent; (b) removing the solvent by freeze-drying.

TITLE OF THE INVENTION

'AMORPHOUS HMG-CoA REDUCTASE INHIBITORS OF DESIRED PARTICLE SIZE'

FIELD OF THE INVENTION

The present invention relates to a process for the production of amorphous HMG-CoA reductase inhibitors of desired particle size.

BACKGROUND OF THE INVENTION

Lovastatin, pravastatin, simvastatin, mevastatin, atorvastatin, fluvastatin and cervastatin and derivatives and analogs thereof are known as HMG-CoA reductase inhibitors and are used as antihypercholesterolemic agents. The majority of them are produced by fermentation using microorganisms of different species identified as species belonging to *Aspergillus*, *Monascus*, *Nocardia*, *Amycolatopsis*, *Mucor* or *Penicillium* genus, some are obtained by treating the fermentation products using the methods of chemical synthesis or they are the products.

The present invention relates to amorphous form HMG-CoA reductase inhibitors, which are useful as a pharmaceutical substance, to the method for its production and isolation HMG-CoA reductase inhibitors, are used for the treatment of hyperlipidemia and hypercholesterolemia, both of which are risk factors for arteriosclerosis and coronary heart disease.

United States Patent 5,273,995, describes that R-form of the ring opened acid form inhibits the biosynthesis of cholesterol. Atorvastatin in its calcium salt form, i.e. amorphous [R-(R*,R*)]-

2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (2: 1) is discussed in literature.

Various United States patents like, 5,003,080; 5,097,045; 5,103,024; 5,124,482; 5,149,837; 5,248,793; 5,280,126; 5,342,952, which are herein incorporated by reference, describe various processes and key intermediates for preparing atorvastatin calcium.

The process mentioned in the above patents does not produce atorvastatin calcium in its amorphous form consistently. Often a mixture of crystalline and amorphous form is obtained which is not suitable for filtration and drying and therefore not a desirable process for large-scale production.

PCT application, WO 97/03959, discloses novel crystalline forms of atorvastatin calcium designated as Form I, Form II, and Form IV and method for their preparation. PCT application WO 97/03960 describes a procedure for converting the crystalline form of atorvastatin to the amorphous form.

The process described in the above mentioned patent involves dissolving the crystalline atorvastatin (form-I) in a non hydroxylic solvent like tetrahydrofuran or mixtures of tetrahydrofuran and toluene, followed by removal of the solvents under high temperature (about 90°C) and high vacuum (about 5mm). This process may not suitable on a large scale as the conditions used for drying may lead to degradation of the product.

PCT application WO 00/71116 claims a process for the preparation of amorphous atorvastatin calcium where the crystalline form is dissolved in a non-hydroxilic solvent is treated with a non-polar hydrocarbon anti-solvent followed by the removal of the solvent to result in the amorphous form.

Pravastatin, which was first reported as a metabolite of compactin in US4,346,227. WO01/43723 describes certain novel forms of pravastatin which are characterized by X-Ray patterns.

SUMMARY OF THE INVENTION

It is desirable to have a process, which provides amorphous HMG-CoA reductase inhibitor using a procedure, which can be readily scaled up to a commercial scale. The present invention describes a process, which is ideal for large scale production of amorphous HMG-CoA reductase inhibitor.

The present invention provides a process for the preparation of amorphous HMG-CoA reductase inhibitor and hydrates thereof of desired particle size, which comprises:

(i) dissolving the heterogeneous mixture of HMG-CoA reductase inhibitor in a hydroxylic solvent and

(ii) removing the solvent to obtain amorphous HMG-CoA reductase inhibitor.

The process further comprises

(iii) subjecting the amorphous HMG-CoA reductase inhibitor to milling.

The solvent is removed by freeze drying or spray drying.

The amorphous HMG-CoA reductase inhibitor has a particle size of 1 to 150 microns.

The hydroxylic solvent solvent in step (i) is methanol.

The HMG-CoA reductase inhibitor is a statin, preferably, atorvastatin or pravastatin having a particle size of 1 to 150 microns.

Major advantages of the present invention compared to the prior art processes are:

i. Produces amorphous HMG-CoA reductase inhibitor consistently.
ii. Results in the final product of desired particle size.
iii. Avoids the necessity to remove solvents.
iv. Simpler and faster filtration.
v. Easy to operate on large-scale.
vi. Avoids the use of hydrocarbons.

The present invention thus provides a simple and novel process for the preparation of amorphous atorvastatin calcium and hydrates thereof. The starting material used in the instant invention comprises of a mixture of both amorphous and crystalline forms – henceforth referred to as heterogeneous mixture.

BRIEF DESCRIPTION OF THE ACCOMPANYING FIGURES

Figure 1 is the diffractogram of amorphous atorvastatin calcium. The horizontal axis represents 2θ and the vertical axis corresponds to peak intensity.

Figure 2 is the diffractogram of amorphous pravastatin. The horizontal axis represents 2θ and the vertical axis corresponds to peak intensity.

The present invention is illustrated by the following examples, which an intended to limit the effective scope of the claims.

DETAILED DESCRIPTION OF THE INVENTION

Major advantages of the present invention compared to the prior art processes are:

i. Produces amorphous HMG-CoA reductase inhibitor consistently.
ii. Results in the final product of desired particle size.
iii. Avoids the necessity to remove solvents.
iv. Simpler and faster filtration.
v. Easy to operate on large-scale.
vi. Avoids the use of hydrocarbons.

The present invention thus provides a simple and novel process for the preparation of amorphous atorvastatin calcium and hydrates thereof. The starting material used in the instant invention comprises of a mixture of both amorphous and

crystalline forms – henceforth referred to as heterogeneous mixture.

The present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

EXAMPLES

Example 1

[R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Amorphous Atorvasatin calcium).

A heterogenous mixture of atorvastatin (5g) was added to methanol (100ml) and the resulting reaction mixture was freeze dried to afford amorphous atorvastatin.

The particle size as measured by malvern particle size analyser gave the following pattern:

D_{10}	3 microns
D_{50}	9 microns
D_{90}	16 microns

Example 2

[1S-([1α(β*,δ*)2α,6α,8B(R*),8aα]]-1,2,6,7,8,8a-hexahydro-β,δ,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-1-naphthalene heptanoic acid sodium salt (Amorphous Pravastatin)

A heterogenous mixture of pravastatin sodium (5g) was added to methanol (100ml) and the resulting reaction mixture was spray dried to afford amorphous pravastatin sodium. The amorphous pravastatin sodium so obtained was milled using an air jet mill

The particle size as measured by malvern particle size analyser gave the following pattern:

D10	3 micron
D50	11 micron
D90	19 micron

Example 3

[1S-([1α(β*,δ*)2α,6α,8B(R*),8aα]]-1,2,6,7,8,8a-hexahydro-β,δ,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-1-naphthalene heptanoic acid sodium salt (Amorphous Pravastatin)

A heterogenous mixture of pravastatin sodium (5g) was added to water (100ml) and the resulting reaction mixture was spray dried to afford amorphous pravastatin sodium. The amorphous pravastatin sodium so obtained was milled using an air jet mill. The particle size as measured by malvern particle size analyser gave the following pattern:

D10	2 micron
D50	4 micron
D90	10 micron

Example - 4

[R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Amorphous Atorvasatin calcium).

A heterogenous mixture of atorvastatin (5g) was added to methanol (100ml) and the resulting reaction mixture was spray dried to afford amorphous atorvastatin.

The particle size as measured by malvern particle size analyser gave the following pattern:

D_{10}	1 microns
D_{50}	6 microns
D_{90}	11 microns

Example 5

[1S-([1α(β*,δ*)2α,6α,8B(R*),8aα]]-1,2,6,7,8,8a-hexahydro-β,δ,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-1-naphthalene heptanoic acid sodium salt (Amorphous Pravastatin)

A heterogenous mixture of pravastatin sodium (5g) was added to methanol (100ml) and the resulting reaction mixture was freeze dried to afford amorphous pravastatin sodium. The amorphous pravastatin sodium so obtained was milled using an air jet mill

The particle size as measured by malvern particle size analyser gave the following pattern:

D10 2 micron

D50	8 micron
D90	16 micron

X-ray powder diffraction pattern (Figure 1 and 2 as shown in the accompanied drawings) demonstrates the amorphous nature of the product.

WE CLAIM:

1. A process for the preparation of amorphous HMG-CoA reductase inhibitor and hydrates thereof of desired particle size, which comprises:

(i) dissolving the heterogeneous mixture of HMG-CoA reductase inhibitor in a hydroxylic solvent and

(ii) removing the solvent to obtain amorphous HMG-CoA reductase inhibitor by freeze drying

2. The process of claim 1, further comprising

(iii) subjecting the amorphous HMG-CoA reductase inhibitor to milling.

3. The process of claim 1 wherein the solvent is removed by spray drying instead of freeze drying.

4. The process of claim 1, wherein the amorphous HMG-CoA reductase inhibitor has a particle size of 1 to 150 microns.

5. The process of claim 1, wherein the hydroxylic solvent solvent in step (i) is methanol.

6. The process of claim 1, wherein the HMG-CoA reductase inhibitor is a statin.

7. The process of claim 6, wherein the HMG-CoA reductase inhibitor is atorvastatin or pravastatin.

8. HMG-CoA reductase inhibitor of particle size 1 to 150 microns.

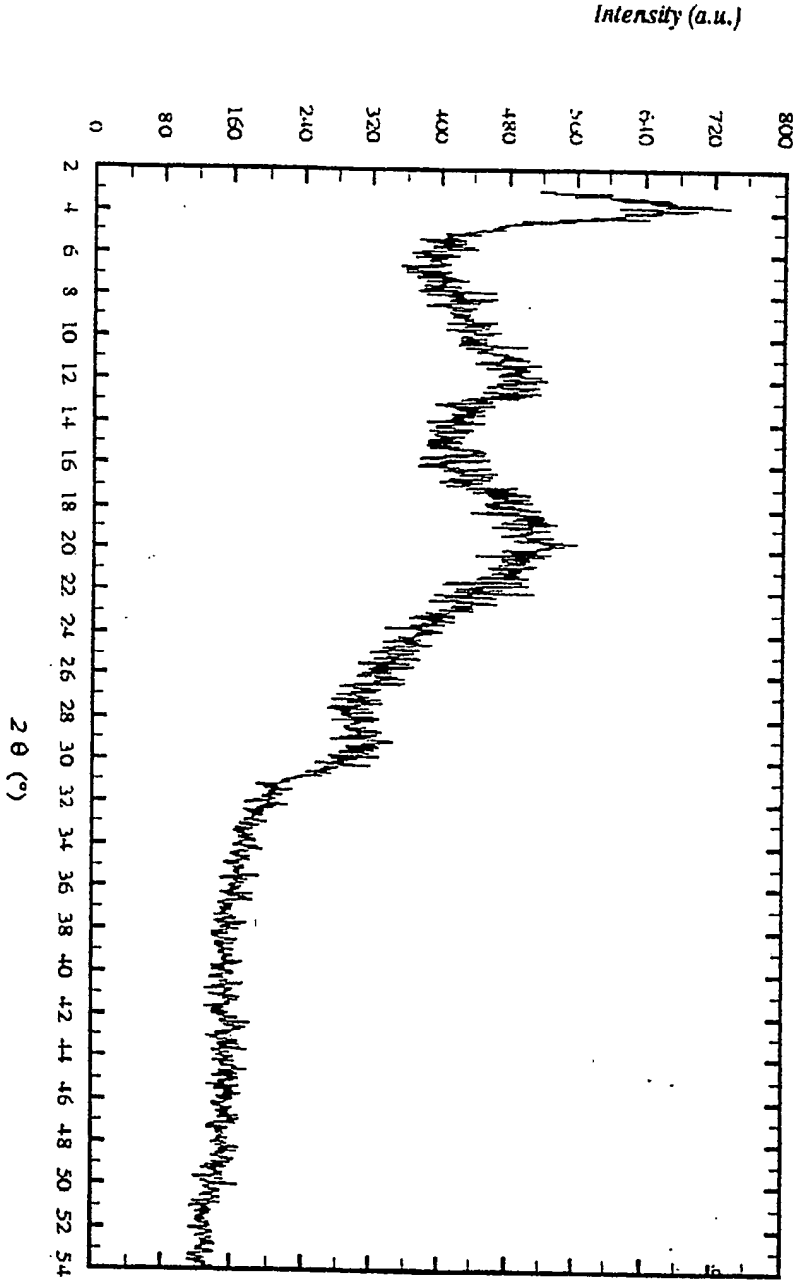

FIGURE 1

ATORVASTATIN CALCIUM

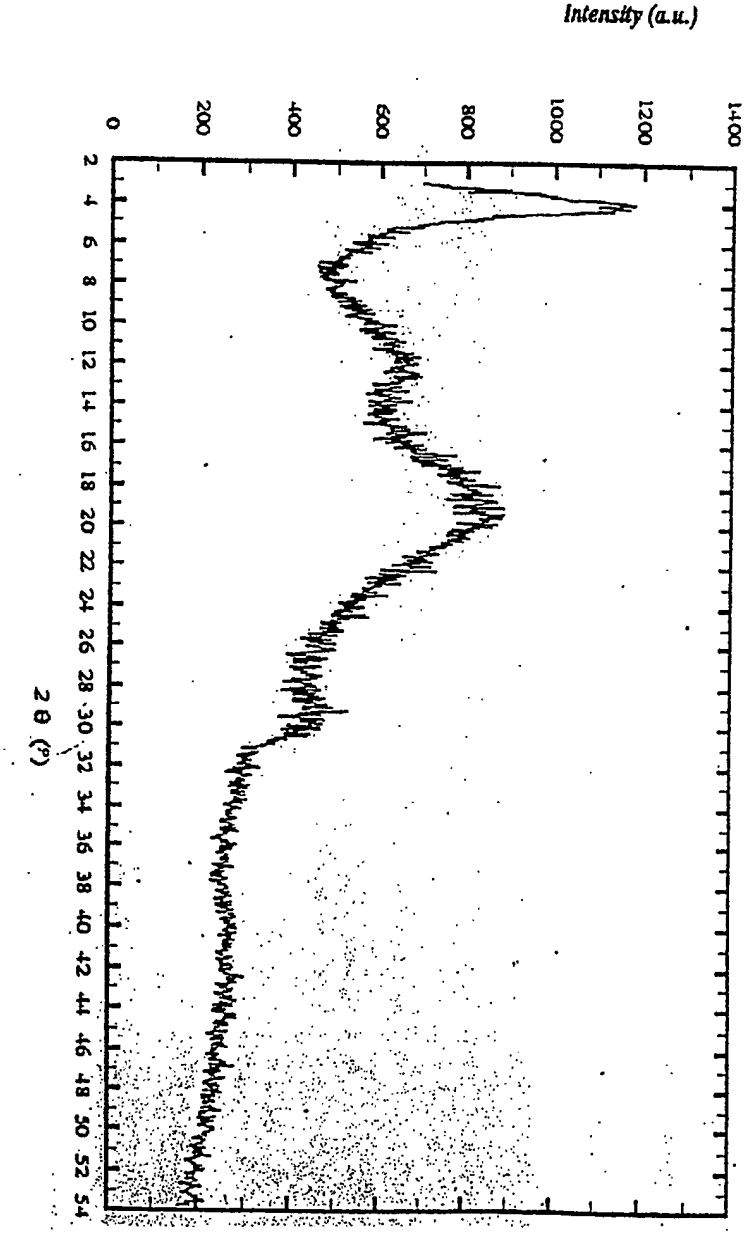
Intensity (a.u.)
0
200
400
600
800
1000
1200
1400
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54
2θ (°)
PRAVASTATIN SODIUM

FIGURE 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN02/00045

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: C07C 69/732; C07D 207/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN FILE CA, Medline,WPIDS using keywords vastatin, amorphous

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	WO 01/42209 A1 (LEK PHARMACEUTICAL AND CHEMICAL COMPANY D.D) 14 June 2001	
X	See page 4 line 10 to page 5 line 2, page 7, claims 1 and 2	8
A		1-7
	WO 01/28999 A1 (EGIS GYOGYSZERGYAR RT) 26 April 2001	
X	See pages 4, 6, examples 1, 2	1-8
	WO 01/10813 A1 (LEK PHARMACEUTICAL AND CHEMICAL COMPANY D.D.) 15 February 2001	
X	See page 2 line 24 to page 3 line 3, page 7 line 26 to page 8 line 28	8
A		1-7

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 June 2002	25 JUN 2002
Name and mailing address of the ISA/AU	Authorized officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	CHRISTINE BREMERS Telephone No : (02) 6283 2313

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN02/00045

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	WO 00/53566 A1 (MERCK & CO., INC.) 14 September 2000	
X	See examples 1, 14 claim 31	8
A		1-7
	WO 97/03958 A1 (WARNER-LAMBERT COMPANY) 6 February 1997	
X	Page 2 lines 29-30	8
A	See page 11, example 2	1-7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN02/00045

Box I **Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos :
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos :
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos :
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II **Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

Claims 1-7 relate to a specific process for preparing amorphous HMG-CoA reductase inhibitor.
Claim 8 relates to HMG-CoA reductase inhibitor or particle size 1 to 150 microns, however produced.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IN02/00045

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Member					
WO 9703958	AU	64841/96	BG	102186	BR	9610567
	CA	2220458	CN	1190957	CZ	9800123
	EE	9800016	EP	848704	HR	960313
	HU	9901687	IL	122162	NO	980208
	NZ	312906	PL	324532	SK	59/98
	US	6121461				

END OF ANNEX